binding ligands comprises a second label.

32. A method according to claim 8 or 29, wherein a first population of decoder binding ligands is contacted with the array to identify the location of at least a first population of bioactive agents; and

subsequently, a second population of decoder binding ligands is contacted with the array to identify the location of at least a second population of bioactive agents.

33. A method according to claim 8 or 29, wherein said plurality of decoder binding ligands comprises at least a first and a second subpopulation of decoder binding ligands.

34. A method according to claim 8, 13 or 14, wherein said discrete sites are wells.- -.

REMARKS

Claims 8-14 and 16-33 are pending. For the Examiner's convenience a copy of the currently pending claims is attached hereto. Claims 8, 13 and 14 are amended. Support for the amendments is found throughout the specification including p. 5, line 21-22 and 30. Support for new claim 19 is found at p. 21, line 36 to p. 22, line 10. Support for new claim 20 is found at p.7, line 34. Support for new claim 21 is found at p. 7, lines15-22. Support for new claim 22 is found at p. 7, line 34. Support for new claim 23 is found at p. 10, line 34-35. Support for new claim 24 is found at p. 10, line 21–22. Support for new claim 25 is found at p. 18, line 8. Support for new claim 26 is found at p. 17, lines 28-35. Support for new claim 27 is found at p. 17, lines 28-35. Support for new claim 28 is found at p. 18, lines 11-12. Support for new claim 29 is found throughout the specification and in claim 8 as filed. Support for new claim 32 is found at p. 26, lines 20-21 Support for new claim 33 is found at p. 24, lines 35-37.

Support for new claim 34 is found throughout the specification as filed, for example at p. 7, lines 29-34.

INTERVIEW

Applicants acknowledge and thank the Examiner for the helpful interview on November 3, 2000.

IDS

Applicants note that the Examiner indicates that references 1-14 of the IDS filed December 6, 1999 appear to be missing from U.S. Application 09/189,543, where the documents were filed, and therefore have not been considered. Applicants are submitting herein all but one of these references. This one reference will be forwarded to the Office promptly, as indicated on the enclosed Information Disclosure Statement. Applicants respectfully request the Examiner to consider these references.

RESPONSE TO REJECTIONS

Response to Rejection Under 35 U.S.C. § 102

Currently pending Claims 6-14 are rejected under 35 U.S.C. § 102 (b) and (e) as being anticipated by Ekins et al (U.S. Patent No 5,516,635). Basically, the Examiner suggests that Ekins et al disclose the placement of tagged microspheres onto a surface to form an array upon which multiple binding assays may performed. Moreover, the Examiner suggests that Ekins discloses that the microspheres contain bioactive agents, identifier binding ligands and decoder binding ligands which identify the bioactive agents. Applicants respectfully traverse.

Ekins is directed to binding assays employing labeled microspheres. Ekins discloses spotting a capture binding agent on a surface and detecting a target that is

immobilized to the capture binding agent with labeled (preferably fluorescently labeled) microspheres. The purpose of the microspheres is to amplify the signal to allow the detection of low amounts of target. The microspheres contain a developing binding agent that binds the capture binding agent, thereby immobilizing the microspheres on the array.

In contrast, Claim 8 is directed to a method of decoding an array. The method includes providing an array composition comprising a substrate with a patterned surface comprising discrete sites, and a population of microspheres, wherein the microspheres are randomly distributed on the surface. Finally the method includes adding a plurality of decoding binding ligands to the array composition to identify the location of at least a plurality of the bioactive agents. The decoding binding ligands of the present invention must be initially physically distinct from the microspheres of the array for the invention to work.

As the Examiner is aware, anticipation under 35 U.S.C. § 102 requires that "[f]or a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference." In re Bond, 15 USPQ2d 1566, 1567 (Fed. Cir. 1990).

With respect to Claim 8, Applicants note that Ekins fails to teach randomly distributing microspheres on a patterned substrate. That is, the microspheres of Ekins bind to specific locations on the array because of the capture binding agent that is spotted on the array.

In addition, Applicants note that the claim 8 describes adding both microspheres and decoder binding ligands; these are independent elements [1]. Accordingly, Applicants submit that Ekins fails to teach each and every element of claim 8; and thus,

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[1]However, it should be noted that in some circumstances, the decoder binding ligand can be attached to a second bead; see the specification at p. 17, lines 11-12.

the rejection should be withdrawn.

Claim 13 is directed to a method of determining the presence of a target analyte in a sample comprising contacting the sample with a composition comprising a substrate with a patterned surface comprising discrete sites and a population of microspheres wherein the microspheres are randomly distributed on the surface such that the discrete sites contain microspheres and determining the presence or absence of the target analyte.

Again Applicants submit that Ekins fails to teach random distribution of microspheres on an array. In addition, Ekins teaches that the microspheres are not randomly distributed because the microspheres associate at sites to which they are targeted as a result of binding to the spotted capture binding agent. Accordingly, Applicants submit that Ekins fails to teach every limitation and thus does not anticipate claim 13.

With respect to claim 14, the claim requires random distribution of microspheres on an array. In addition, claim 14 recites that the microspheres contain a bioactive agent and an identifier binding ligand that will bind a decoder binding ligand such that the identification of the bioactive agent can be elucidated. However, Ekins teaches microspheres that contain only an antibody or nucleic acid (a bioactive agent) and a label.

The Examiner suggests that Ekins teaches microspheres that contain both nucleic acids (bioactive agents) and proteins (which serve as identifier binding ligands and decoder binding ligands)(see p. 2 last paragraph of the June 6, 2000 Office Action). Applicants respectfully disagree with this characterization.

The purpose of Ekins is to provide labeled microspheres with an agent that will bind to a target molecule. Ekins notes that nucleic acids can be used to bind target nucleic acids and that antibodies can be used to bind to particular target molecules inlcuding double stranded DNA (see Figures 3-5). However, Ekins does not teach the

use of microspheres with a bioactive agent and an identifier binding ligand that will bind to a decoder binding ligand. That is, in present claim 14, both a bioactive agent and an identifier binding ligand are required on a microsphere. Accordingly, Applicants submit that Ekins fails to anticipate claim 14.

The Examiner's attention is further drawn to new claims 22 and 34 which describe that the substrate is a fiber optic bundle and that the discrete sites are wells, respectively. Applicants submit that Ekins fails to teach a substrate that is a fiber optic bundle. Further, Applicants submit that Ekins fails to teach a substrate wherein the discrete sites are wells.

Response to Rejection under 35 U.S.C. § 103

Claims 1-18 are rejected under 35 U.S.C. § 103 as being unpatentable over Ekins in view of Vergne et al (Analytical Biochemistry, vol. 255(1), pp. 127-132 (1 January 1998).

As a preliminary matter, it appears that this rejection was intended for claim 15, now cancelled without prejudice or disclaimer.

As described above Ekins teaches the use of labeled microspheres to detect a target analyte on a substrate. Vergne teaches a method of phagosome pH detection using double labeling of cells with a ph-sensitive and ph-insensitive probe. Basically the Examiner suggests that it would have been obvious to one of ordinary skill in the art to replace the dyes of Ekins with the dyes of Vergne thereby rendering obvious the presently claimed invention. Applicants respectfully traverse the rejection.

Applicants note that there are three requirements to establish a *prima facie* case of obviousness. These include that "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art

reference (or references when combined) must teach or suggest all the claim limitations" (MPEP § 2143).

To this end, Applicants respectfully submit that neither reference provides the motivation for the combination. Although the Examiner suggests that motivation is found in the teaching of Ekins because Ekins teaches dyes that can be differentiated from each other, Applicants submit that nowhere in Ekins is there a suggestion to monitor differences in pH or use dyes with a different pKa.

The Examiner also suggests that motivation is found in Vergne because Vergne teaches the advantages of being able to distinguish subpopulations of cells using dyes with different pKa's. However, there is no teaching or suggestion in Vergne of the desire to use these dyes in any format outside the phagosome.

As such, Applicants submit that the references alone or in combination fail to provide motivation for the skilled artisan to combine the references.

In addition, Applicants submit, as described above, that neither the references individually or in combination teach random distribution of microspheres on a substrate. As such, Applicants submit that not only is there no motivation for the combination of the references, but even when made, the combination fails to teach each element of the claims.

Accordingly, Applicants submit that none of the cited references taken alone or in combination renders the claimed invention obvious to one of skill in the art at the time the invention was made. Accordingly, a *prima facie* case of obviousness has not been made, and the rejection should be withdrawn.

CONCLUSION

Applicants submit that the claims as amended are in form for immediate allowance and the Examiner is respectfully requested to early notification to that effect.

The Examiner is invited to contact the undersigned at (415) 781-1989 if any issues may be resolved in that manner.

Respectfully submitted,

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